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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,797	01/22/2002	David Beach	CSHL-P03-010	7431

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/055,797	BEACH ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-108 and 111-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-108, 111-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/02/03, 07/01/03*. 1/10/05, 8/18/05, 1/24/04 8/2/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 08/11/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/19/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 8/11/2005, claims 83-108 and 111-124 are pending in the application. Applicant has canceled claims 109-110.

Priority

The claims of the instant application do not receive the benefit of the earlier applications PCT/US01/108435, 60/243,097 and 60/189,739 because the prior applications do not provide adequate support for the claims of the instant application.

The instant claims are drawn a method of attenuating expression of a target gene in a mammalian cells comprising introducing into mammalian cells suspended in culture a library of single-stranded hairpin RNA wherein each hairpin RNA comprises self-complementary sequences of 19 to 100 nucleotides that form duplex regions and hybridize to a target gene and further is a substrate for cleavage by a RNase III enzyme, does not produce general sequence-independent killing and reduces expression of said target gene

The prior applications disclose methods of gene silencing in cells provoked by a double-stranded RNA (dsRNA) that is sequence specific to a target gene. Although the provisional application discloses a method of attenuation of a target gene using dsRNA, the provisional application does not disclose the single-stranded self-complementary RNA are 19-100 nucleotides in length.

If Applicant believes the prior applications provide support then Applicant must point, with particularity, to where such support can be found in the specification of the prior applications.

Therefore, the priority date granted to the instant claims is 1/22/2002, the filing date of the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 95-98 and 101 are provisionally rejected under the judicially created doctrine of double patenting over claim 25-28 of copending Application No. 10/350,798. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 25-28 of '798 application has overlapping scope with claims 95-98 and 101 of the instant application.

Claims 25-28 of '798 are drawn to a method for generating a variegated library of short interfering double-stranded RNA (siRNA) by providing an *in vitro* transcription system which uses a RNA polymerase. Claims 95-98 and 101 of the instant application are drawn to producing a variegated library of hairpin RNA which is transcribed *in vitro* and utilizes a RNA polymerase.

Therefore, claims 25-28 of '798 have the same limitations as claims 95-98 and 101 of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83-108 and 111-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 83-108 and 111-124 are drawn a method of attenuating expression of a target gene in a mammalian cells comprising introducing into mammalian cells suspended in culture a library of single-stranded hairpin RNA wherein each hairpin RNA comprises self-

complementary sequences of 19 to 100 nucleotides that form duplex regions and hybridize to a target gene and further is a substrate for cleavage by a RNase III enzyme, does not produce general sequence-independent killing and reduces expression of said target gene.

The specification, on page 5, discloses the dsRNA "...is at least 20, 21, 22, 25, 50, 100, 200, 300, 400, 500, 800 nucleotides in length." Example 1 in the specification discloses a method of RNAi gene silencing using 540 or 400 nucleotide dsRNAs and state "Double-stranded *cyclin E* RNAs of 50 or 100 nucleotides were inert...."

The amendment to the claims filed on 12/17/2004 adding the limitation "19 to 100 nucleotides" and "does not produce a general sequence-independent killing of the mammalian cells" represents a departure from the claims as originally filed and further the specification does not contemplate a method of attenuating expression of a target gene in a mammalian cells comprising introducing a library of hairpin RNA further comprising self-complementary regions of 19 to 100 nucleotides that for a duplex that hybridizes to a target gene and does not produce a general sequence-independent killing of the mammalian cell.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Therefore, the priority date granted to claim 83-108 and 111-124 are considered, for purposes of prior art, to be 01/22/2002, which is the filing date of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 83-88, 90-100, 102-108, 113-115, 120, 123-124 rejected under 35 U.S.C. 102(e) as being anticipated by Barber et al. (U.S. Patent No. 6,605,429) as evidence by Hammond et al. (Nature 2000).

Claims 83-84 are drawn to a method of attenuating expression of a target gene in a mammalian cell comprising introducing into said mammalian cell, suspended in culture, a library of single-stranded hairpin RNA wherein each hairpin RNA comprises self-complementary sequences of 19 to 100 nucleotides that form duplex regions and hybridize to a target gene and further is a substrate for cleavage by a RNase III enzyme, does not produce general sequence-independent killing and reduces expression of said target gene or a plurality of different target genes. Claims 85-87 recite the library of hairpin RNA are arrayed on a solid substrate or arrayed in wells of a multi-well plate and further identifying hairpin RNA which produce a detected phenotype. Claims 88-109 recite the hairpin RNA is transcribed from an expression construct introduced into mammalian cells as listed by transfection or microinjection and further wherein the hairpin RNA is operably linked to a regulatory sequences comprising a polymerase III promoter, a bacteriophage promoter, a cellular promoter or a T7, T3 or SP6 promoter. Claims 111-115, 120 and 123-124 recite the target gene is an endogenous, heterologous or pathogenic gene and further the self complementary sequences are 20-50 nucleotides in length.

Barber et al. teach a method of attenuating expression of a target gene (see column 32 lines 21-45) in mammalian cells using a library of single-stranded RNA 50 to 54 nucleotides

comprising a self-complementary sequence that forms a duplex region and hybridizes with a specific target gene sequence to attenuate expression (see column 5, lines 59-67). It is noted that Hammond et al. teach attenuation of a target gene by a duplex RNA is mediated by an RNAse III enzyme (see entire article, especially Methods page 295). Barber et al. further teach the hairpin RNA is transcribed from an expression cassette (see column 16 lines 10-50) and further the expression cassette comprises a coding region for said hairpin RNA that is operably linked to a promoter wherein said promoter is an inducible promoter or a RNA polymerase (e.g. T7 polymerase) (see column 10 lines 26-54 and column 35 lines 31-34). Further, Barber et al. teach the hairpin RNA can be transfected into said mammalian cells or microinjected into said mammalian cells (see column 17 lines 32-56) wherein said mammalian cells are stem cells (see column 29 lines 36-40) somatic or immortalized human cells (see column 17 and 42, lines 10-22 and 59-67, respectively). Barber et al. additionally teach the library of hairpin RNA can be arrayed on a solid support (see column 33, lines 20-50) or arrayed in wells of multi-well plate (see column 45, lines 45-66).

Thus Barber et al. anticipates claims 83-88, 90-100, 102-108, 113-115, 120, 123-124 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 83-87, 95-98, 102-108, 111-115 and 120-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US Patent Number 6,506,559) in view of Agrawal et al. (WO 94/01550) and as evidenced by Tuschl et al. (US 2004/0229266).

Claims 83-84 are drawn to a method of attenuating expression of a target gene in a mammalian cells comprising introducing into mammalian cells suspended in culture a library of single-stranded hairpin RNA wherein each hairpin RNA comprises self-complementary sequences of 19 to 100 nucleotides that form duplex regions and hybridize to a target gene and further is a substrate for cleavage by a RNase III enzyme, does not produce general sequence-independent killing and reduces expression of said target gene or a plurality of different target genes. Claims 85-87 recite the library of hairpin RNA are arrayed on a solid substrate or arrayed in wells of a multi-well plate and further identifying hairpin RNA which produce a detected phenotype. Claim 95-98 recites the hairpin RNA comprising a RNA polymerase promoter, a bacteriophage promoter or a T7, T3 or SP6 promoter. Claims 102-108 and 111-115 recite the expression of the target gene is attenuated by at least 33 or 90 percent relative to expression of cells not treated with the hairpin RNA and further wherein the target gene is an endogenous, heterologous or pathogenic gene. Claims 120-124 recite the self-complementary sequence of the hairpin RNA is 20-50 or 29 nucleotides in length.

Fire et al. disclose a method of attenuating expression of a target gene in mammalian cells (see column 8, lines 12-19), *in vitro*, comprising a library of duplex RNA (see column 12, lines 49-54) wherein the RNA can be formed by a single self-complementary RNA or two complementary RNA strands (see column 7, lines 42-44) and wherein inhibition is sequence specific (see column 7, lines 49-52). Fire et al. teach the library of duplex RNA can be arrayed

on a solid support or wells of a microtiter plate (see column 12, lines 55-61). Fire et al. additional teach the target gene is attenuated by at least 33 or 90 percent relative to expression of cells not treated with the RNA duplex, RNA duplex can comprise modifications to the phosphate-sugar backbone or nucleoside residues, the modifications can block the activity of adenosine deaminase (see column 7, line 14-39) and the RNA is a transcriptional product of a RNA polymerase, a bacteriophage RNA promoter or a T7, T3 or a SP6 promoter (see column 7, lines 5-15). Fire et al. further discloses the target gene can be an endogenous gene or a pathogen (see column 6, lines 44-51) and the cells having the target gene may be from the germ cell line, somatic cell line, stem cell line or immortalized cell line (see column 8, line 12-62). Fire et al. does not disclose a nucleotide length of 19 to 100.

Agrawal et al. teach a single stranded RNA comprising a self-complementary sequence 19-100 in length and more specifically teach a single-strand RNA 29 nucleotides in length (see Figure 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a single-stranded RNA between 19-100 nucleotides in length, at taught by Agrawal et al. in the method of attenuating gene expression, as taught by Fire et al.

One would have been motivated to use a use a single-stranded RNA between 19-100 nucleotides in length attenuate gene expression because Tuschl et al. teach duplex RNA between 19 to 100 nucleotides are capable of mediating target specific attenuation of gene inhibition.

Finally, one would have a reasonable expectation of success because Fire et al. teach a method of attenuating gene expression using single stranded self-complementary RNA, Agrawal teach single stranded self-complementary RNA between 19-100 nucleotides in length and Tuschl

et al. teach duplex RNA between 19-100 and more specifically 19-25 efficiently mediate target-specific attenuation of gene inhibition by an RNAse III enzyme.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 83-108, 113-115, 120, 123-124 rejected under 35 U.S.C. 103(a) as being unpatentable over Barber et al. (U.S. Patent No. 6,605,429) in view of Good et al. (Gene Therapy 1997), Lipardi et al. (Cell 2001) in further view of Bennett et al. (U.S. Patent No. 5,998,148) and as evidence by Hammond et al. (Nature 2000).

Claims 83-84 are drawn to a method of attenuating expression of a target gene in a mammalian cells comprising introducing into mammalian cells suspended in culture a library of single-stranded hairpin RNA wherein each hairpin RNA comprises self-complementary sequences of 19 to 100 nucleotides that form duplex regions and hybridize to a target gene and further is a substrate for cleavage by a RNase III enzyme, does not produce general sequence-independent killing and reduces expression of said target gene or a plurality of different target genes. Claims 85-87 recite the library of hairpin RNA are arrayed on a solid substrate or arrayed in wells of a multi-well plate and further identifying hairpin RNA which produce a detected phenotype. Claims 88-109 recite the hairpin RNA is transcribed from an expression construct introduced into mammalian cells as listed by transfection or microinjection and further wherein the hairpin RNA is operably linked to a regulatory sequences comprising a polymerase III promoter, a bacteriophage promoter, a cellular promoter or a T7, T3 or SP6 promoter or a U6

promoter. Claims 116-115 recite the self-complementary sequences hybridize to a non-coding sequence of a target gene.

Barber et al. teach a method of attenuating expression of a target gene (see column 32 lines 21-45) in mammalian cells using a library of single-stranded RNA 50 to 54 nucleotides comprising a self-complementary sequence that forms a duplex region and hybridizes with a specific target gene sequence to attenuate expression (see column 5, lines 59-67). It is noted that Hammond et al. teach attenuation of a target gene by a duplex RNA is mediated by an RNAse III enzyme (see entire article, especially Methods page 295). Barber et al. further teach the hairpin RNA is transcribed from an expression cassette (see column 16 lines 10-50) and further the expression cassette comprises a coding region for said hairpin RNA that is operably linked to a promoter wherein said promoter is an inducible promoter or a RNA polymerase (e.g. T7 polymerase) (see column 10 lines 26-54 and column 35 lines 31-34). Further, Barber et al. teach the hairpin RNA can be transfected into said mammalian cells or microinjected into said mammalian cells (see column 17 lines 32-56) wherein said mammalian cells are stem cells (see column 29 lines 36-40) somatic or immortalized human cells (see column 17 and 42, lines 10-22 and 59-67, respectively). Barber et al. additionally teach the library of hairpin RNA can be arrayed on a solid support (see column 33, lines 20-50) or arrayed in wells of multi-well plate (see column 45, lines 45-66). Barber et al. does not teach an expression construct comprising a U6 promoter, does not teach the hairpin RNA is a transcription product of a RNA-dependent RNA polymerase (RdRp) and further does not teach targeting a non-coding sequence of the target gene.

Good et al. teach an expression construct comprising a U6 promoter and a coding sequence for a hairpin RNA (see Figure 1). Lipardi et al. teach generation of RNA using an RdRp (see Figure 7). Bennett et al. teach targeting the non-coding region of a target gene and specifically teach the non-coding region comprises intronic sequences (see column 4, lines 20-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the expression construct comprising a U6 promoter, as taught by Good et al. for the expression of a hairpin RNA, as taught by Barber et al. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transcribe duplex RNA using an RdRp. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to target the non-coding region of a target gene in a method of attenuating gene expression of a target gene.

One would have been motivated to use an expression construct comprising a U6 promoter because Good et al. specifically teach expression constructs comprising a U6 promoter efficiently transcribe hairpin RNAs, stabilize RNAs against degradation and direct the RNAs to the part of the cell where it can be most efficient (see Abstract). Further, one would have been motivated to make transcribe RNA using RdRp because RdRp is shown to mediate the incorporation of RNA into dsRNA (see page 297, column 2 last paragraph). Additionally, one would have been motivated to target a non-coding region of a target gene and specifically target intronic sequences of the target gene because Bennett et al. teach targeting non-coding regions and more specifically intronic sequences are "particularly useful in situations where aberrant splicing is implicated in disease...."

Finally, one would have a reasonable expectation of success because Good et al. teach target specific attenuation of gene expression using hairpin RNA generated from an expression construct comprising a U6 promoter (see page 48), Lipardi teach an RdRp transcriptional RNA efficiently attenuates gene expression (see Figure 7) and Bennett et al. teach attenuation of gene expression using complementary RNA targeting non-coding regions of a target gene (see Table 1).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Double Patenting

The rejection of record of claims 95-98 and 101 under the judicially created doctrine of double patenting over claim 25-28 of copending Application No. 10/350,798 is maintained.

Claim Rejections - 35 USC § 102

The rejection of record of claims 83-124 under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US Patent Number 6,506,559) is withdrawn.

Claim Rejections - 35 USC § 112

The rejection of record of claims 83-124 under 35 U.S.C. 112, first paragraph, as not being enabling for a method of attenuating expression of one or more target genes using a

dsRNA in mammalian cells *in vivo*, is withdrawn in response to Applicant's amendment filed 08/11/2005.

The rejection of record of claims 83-124 under 35 U.S.C. 112 second paragraph as indefinite is withdrawn in response to Applicant's amendment filed 08/11/2005.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

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Kimberly Chong
Examiner
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SEAN McGARRY
PRIMARY EXAMINER